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# Zebrafish (*Danio rerio*) – Tool for Drug Discovery and Development

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**ABSTRACT**

The zebrafish (*Danio rerio*) has become a widely used vertebrate model organism for drug delivery due to its morphological and physiological resemblance to mammals. Zebrafish is a powerful model organism with a combination of forward and reverse genetics, low cost, amenable high throughput and rapid in *In vivo* analysis. It is an ideal complementary model system for drug discovery, as it capable of high throughput screening for discovery of novel drug delivery system. For the past few years, zebrafish has proven a tremendous model to prove clinical efficacy and reducing the time and money in drug discovery. This article reveals the recent importance, innovation and applications of zebrafish in present and future aspects. This review reveals about the potential of zebrafish to contribute to excellent model in the drug discovery, toxicity studies, novel drug targets, validations, screening for new therapeutic compounds and assay development.

## INTRODUCTION

The world of fish pharmacology is now changing quickly. Fish has now been considered as the model organism for conducting different experimental studies, including those of pharmacology and toxicology. A wide variety of experiments and the use of drugs in fish have been elucidated in various literature. The zebrafish (*Danio rerio*) is a small tropical fish (Family- Cyprinidae). Zebrafish has been an important model organism in genetics and toxicological studies. A number of unique features have contributed to its attraction such as it is a very small vertebrate that can be kept in captivity in large number easily. Its generation time is short and most important a single spawning can produce hundreds of offspring's, entire body plan established by 24 hrs post fertilization (hpf)[1]. Recently, Zebrafish crossed the border and metamorphose into a promising tool for drug discovery and development.

### Zebrafish – *In vitro* animal

Zebrafish have emerged as powerful models for drug discovery and biosafety studies because they develop most of the organs found in mammals including those of the nervous, digestive, reproductive, immune and excretory and cardiovascular system[4,5]. Zebrafish is easy to breed zebrafish in embryo and larvae in short span of time (Fig: 01) (small volume of media)[6]. More number of compounds can be studied (Nanogram), zebrafish absorb the compounds through the skin and gills at embryonic stage [7,8,9]. This small fish can be used as a suitable *in vivo* animal model for drug discovery. Nowadays zebrafish is used various pharmacological studies including screening investigation of mechanism of action of biologically active substances, toxicological studies[10].

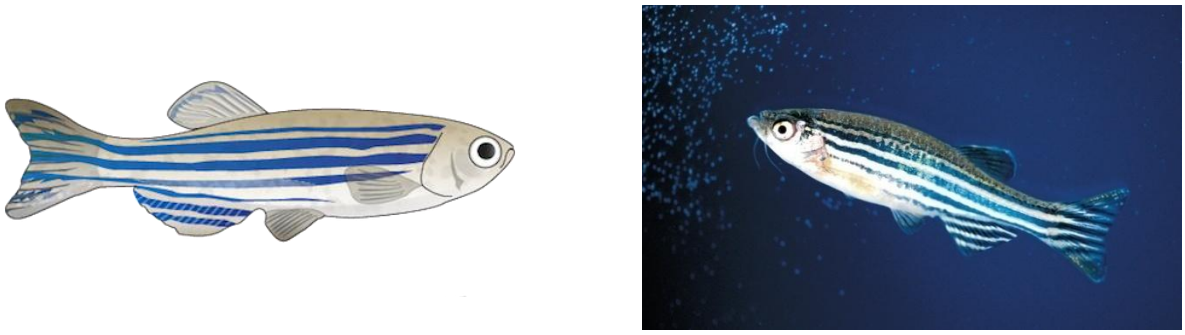

**Fig 01: Zebrafish (*Danio rerio*)**

**Challenges in Drug discovery:**

In predominant drug discovery methodologies for the past 50 yrs have been target centric. The drug development process in it's entirely from compound selection and identification through preclinical studies takes approximately 10 -15 years[2].

A high number of compounds are often filtered out during the preclinical animal testing stage, due to failure meet standards of ADME. More than 70% of compounds in cancer treatment fails in Phase- II clinical trials & 59% discarded in phase – III due to intolerable toxicities.

To overcome this zebrafish has emerged as an ideal complementary model system for drug discovery, capable of high throughput screening for discovering of novel drug for cancer modulations. A small molecule screening in zebrafish could identify genetic mutation, developmental disorders and timing of the chemical action during development[3].

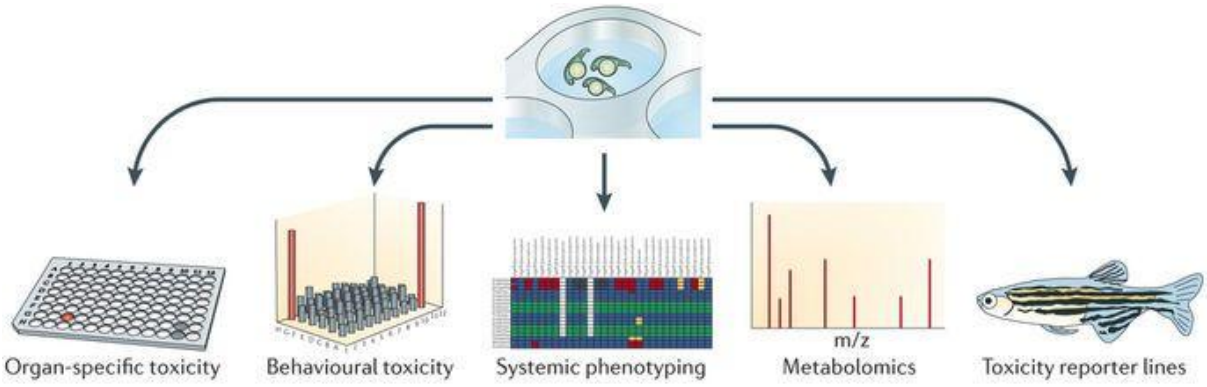


**Fig 02: Zebrafish in drug discovery**

**In cancer- drug discovery:**

Zebrafish can develop any types of tumour with similar morphology and comparable signalling pathway. It is mainly employed in gut, thyroid & liver[11]. Similarly, carcinogens have also been employed by soaked in water along with zebrafish at different concentration and durations. Transgenic zebrafish cancer models also studied by DNA microinjected method. Zebrafish zenograft model in cancer cells and its embryos for anticancer drug screening; cancer drug validation and other oncology studies were employed using zebrafish.

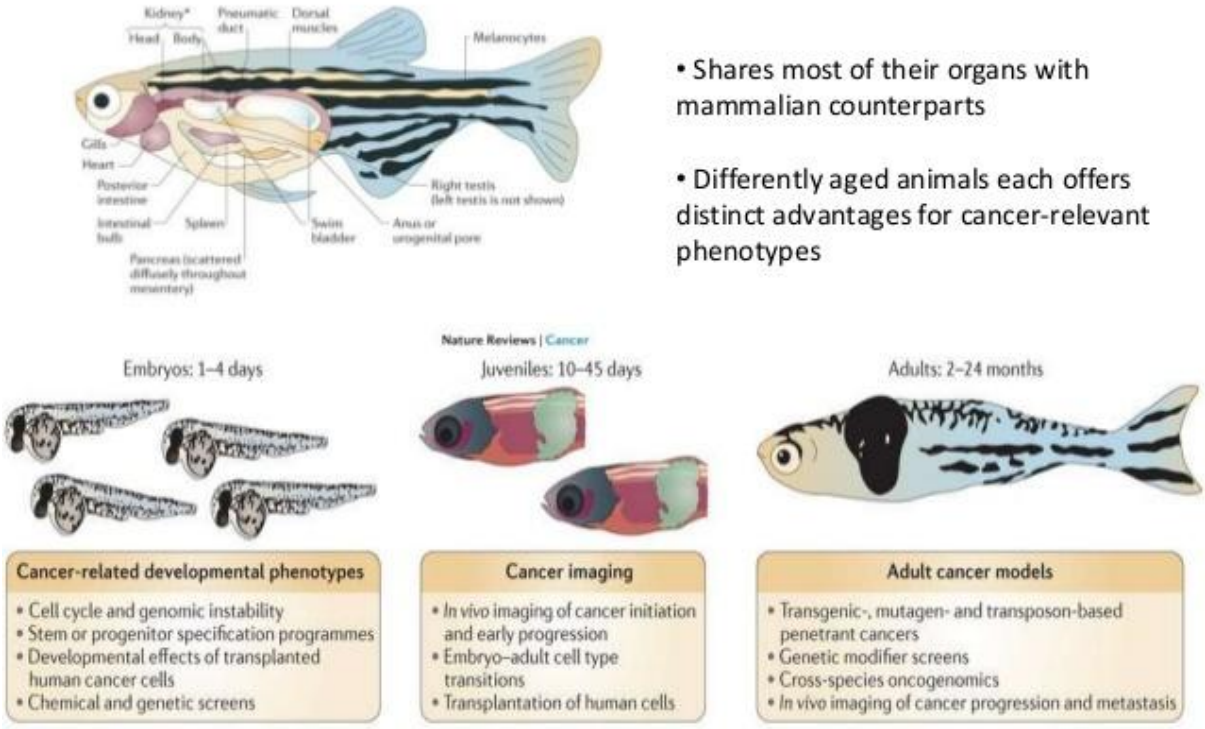


**Fig 03: Zebrafish in cancer drug discovery**

## Zebrafish for High throughput screening of Novel drugs [12]

The identification of cardiovascular drugs is a major risk and challenge nowadays. The diseases are complex mainly involved in multiple cell types and a host systemic factor. The utility of zebrafish in high throughput screening provides a potential approach to overcome the hurdles in drug discovery. There are different techniques have been developed to measure the heart rate, contractility and blood flow at high throughput in the zebrafish. Several assays like optical voltage mapping, calcium imaging, signalling reporters and organelle functions. These techniques are helpful for screening of large scales in new drug discovery.

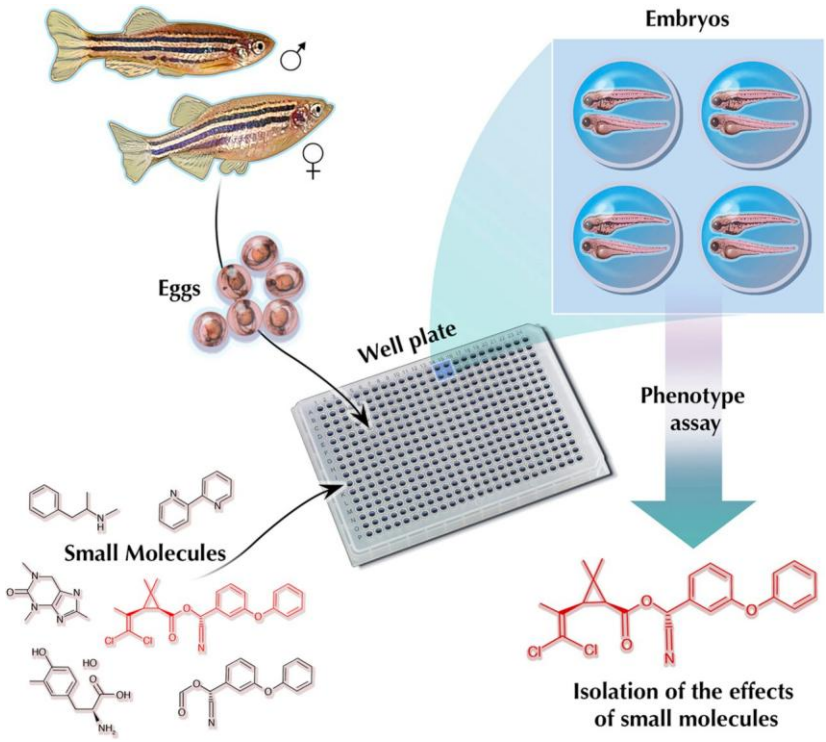


**Fig 04: Zebrafish in High throughput screening**

**Model for Screening of Antidiabetic drugs**

Diabetes mellitus affects the million numbers of people all around the world, it's a life threatening disease which will affect other organs present in our body and also increase in morbidity rate associated with diabetes. Various natural products have shown potential as antidiabetic agents in zebrafish cell based screening systems like fluorescent – tagged glucose bioprobes.

**Table 1: Comparison between zebrafish and rodents for screening antidiabetic compound [13]**

| Sr. No. | ZEBRAFISH | RODENTS |
|---|---|---|
| 1. | They can induce diabetes mellitus by simple immersion in high glucose water.<br>High throughput screening for antidiabetic is possible. | Developed diabetes mellitus within a few days by chemical injection or feeding a high fat diet.<br>High throughput screening for antidiabetic is not possible. |
| 2. | Inexpensive and easier to handle compared to mammalian models. | Expensive and harder to handle due to relatively large size. |
| 3. | Adult and larval zebrafish are suitable for screening studies. | Need ethical issues. |
| 4. | Fluorescence imaging of whole organism is possible for glucose uptake analysis. | Mouse are amendable for fluorescence tracer based imaging. |

## CONCLUSION

Zebrafish genetics similar to humans, it is most powerful tool *in vivo* drug discovery system in lead identification and optimisation of new compounds through high throughput screening and also helpful in pharmacokinetics, toxicological studies of many compounds in short span of time at low costs. In oncology, cancer cell line studies have also been studied. As per the studies more than 70 % similarity is seen in between mammalian and zebra fish[3]. The high degree of conservation between fish and man further established the usefulness of the zebrafish as an important tool for human cancer drug discovery and development.

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